

| | | | |
|--|--|--|--|
| (51) International Patent Classification 6 : C07D 213/30, 213/32, 403/06, A61K 31/44 | | A3 | (11) International Publication Number: WO 98/04528 (43) International Publication Date: 5 February 1998 (05.02.98) |
| (21) International Application Number: PCT/US97/13248 (22) International Filing Date: 29 July 1997 (29.07.97) (30) Priority Data: 08/690,111 31 July 1996 (31.07.96) US | | (US). KRAMSS, Richard, H.; 978 Little Meadow Road, Guilford, CT 06437 (US). HERTZOG, Donald, L.; 421 Warpas Road, Madison, CT 06443 (US). OSTERHOUT, Martin, H.; Apartment 11, 409 Whitney Avenue, New Haven, CT 06511 (US). (74) Agents: GRAY, William, F. et al.; Bayer Corporation, 400 Morgan Lane, West Haven, CT 06516 (US). | |
| (71) Applicants: BAYER CORPORATION [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US). BAYER AKTIENGESSELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE). (72) Inventors: SCHMIDT, Gunter; Pahlkestrasse 63, D-42115 Wuppertal (DE). ANGERBAUER, Rolf; Moospfad 20, D-42113 Wuppertal (DE). BRANDES, Arndt; Pahlkestrasse 5, D-42115 Wuppertal (DE). MULLER-GLIEMANN, Matthias; Holz 24, D-42719 Solingen (DE). BISCHOFF, Hilmar; Am Rohm 78, D-42113 Wuppertal (DE). SCHMIDT, Delf; Am Eckbusch 55b, D-42113 Wuppertal (DE). WOHLFEIL, Stefan; Dorothea-Erxleben-Strasse 31, D-40721 Hilden (DE). SCHOEN, William, R.; 60 Field Brook Road, Madison, CT 06443 (US). LADOUCEUR, Gaetan, H.; 31 Stone Ridge Lane, Branford, CT 06405 (US). COOK, James, H., II; 36 Mallard Cove, East Hampton, CT 06424 (US). LEASE, Timothy, G.; 74 Christopher Lane, Guilford, CT 06437 (US). WOLANIN, Donald, J.; 320 Longmeadow Road, Orange, CT 06477 | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). | |
| | | Published With international search report. (88) Date of publication of the international search report: 11 November 1999 (11.11.99) | |
| (54) Title: SUBSTITUTED PYRIDINES AND BIPHENYLS AS ANTI-HYPERCHOLESTERINEMIC, ANTI-HYPERLIPOPROTEINEMIC AND ANTI-HYPERGLYCEMIC AGENTS | | | |
| (57) Abstract Substituted pyridines of formula (IA) are produced by reaction of suitably substituted pyridylaldehydes with Grignard or Witting reagents, and the resulting products are appropriately reduced. The pyridines of formula (IA) are suitable as active compounds in pharmaceutical products, particularly in pharmaceutical products for the inhibition of cholesterol ester transfer proteins. 3-Heteroalkyl-aryl-substituted pyridines of formula (IB) are produced from pyridines which are correspondingly protected at the hydroxy group and correspondingly substituted. The compounds of formula (IB) according to the invention are suitable as active compounds in pharmaceutical products, particularly pharmaceutical products for the treatment of hyperlipoproteinemia. Substituted pyridines and benzenes of formula (IC) are produced by procedures disclosed herein, and are useful as active ingredients in pharmaceutical products, particularly pharmaceutical products for inhibition of the glucagon receptor, leading to treatment of glucagon-mediated conditions such as diabetes. | | | |

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakhstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LJ | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/13248

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/30 C07D213/32 C07D403/06 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPO

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | EP 0 306 929 A (WARNER-LAMBERT CO.) 15 March 1989 see claims 1-10 | 1-20 |
| Y | EP 0 325 129 A (BAYER AG) 26 July 1989 see claims 1-14 | 1-47 |
| Y | EP 0 325 130 A (BAYER AG) 26 July 1989 cited in the application see claims 1-15 | 1-47 |
| Y | EP 0 444 533 A (E.R. SQUIBB & SONS, INC.) 4 September 1991 see claims 11-4 | 1-10 |
| Y | EP 0 603 699 A (BAYER AG) 29 June 1994 see claims 1-10 | 1-47 |
| | -/- | |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

24 February 1998

Date of mailing of the international search report

06.03.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/13248

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | J. A. ROBL ET AL.: "Phosphorus-Containing Inhibitors of HMG-CoA Reductase. 2. Synthesis and Biological Activities of a Series of Substituted Pyridines Containing a Hydroxyphosphinyl Moiety" J. MED. CHEM., vol. 34, no. 9, 1991, pages 2804-2815, XP002045951 see tables I-IV --- | 1-10 |
| E | EP 0 796 846 A (BAYER AG) 24 September 1997 see claims 1-10 --- | 11-20 |
| X | US 5 169 857 A (BAYER AG) 8 December 1992 see claims 1-9; example 91 --- | 11-20 |
| Y | see claims 1-9 --- | 21-47 |
| P, Y | EP 0 742 208 A (GRELAN PHARMACEUTICAL CO., LTD. & LABORATOIRES FOURNIER S.C.A.) 13 November 1996 see claims 1-12 ----- | 11-20 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/13248

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-10

anti-hypercholesterinemic tetrasubstituted 4-arylpyridines of formula 1A having an alkyl group in 3- and/or 5-position which carries a cyclic moiety

2. Claims: 11-20

anti-hyperlipoproteinemic trisubstituted 3-hydroxymethyl-4-arylpyridines of formula 1B having an heteroalkyl group in the 5-position which carries a cyclic moiety

3. Claims: 21-47

anti-glucemic tetrasubstituted 4-(het)arylpyridines and benzenes of formulae 1A, 1B, 1C and 1D having a hydroxy, trifluoroacetyl or alkyl group in the 5-position which is substituted by a trifluoromethyl or hydroxy group

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/13248

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 306929 A | 15-03-89 | US 4906624 A | 06-03-90 |
| | | AU 2141288 A | 09-03-89 |
| | | DK 497488 A | 09-03-89 |
| | | JP 1121266 A | 12-05-89 |
| | | US 4997837 A | 05-03-91 |
| ----- | | | |
| EP 325129 A | 26-07-89 | DE 3801440 A | 03-08-89 |
| | | AT 111081 T | 15-09-94 |
| | | AU 614810 B | 12-09-91 |
| | | AU 2861389 A | 20-07-89 |
| | | CN 1034716 A | 16-08-89 |
| | | DE 58908290 D | 13-10-94 |
| | | DK 23289 A | 21-07-89 |
| | | ES 2058343 T | 01-11-94 |
| | | FI 92195 B | 30-06-94 |
| | | HU 208691 B | 28-12-93 |
| | | JP 2001478 A | 05-01-90 |
| | | PT 89478 B | 31-12-93 |
| | | US 5502057 A | 26-03-96 |
| | | US 4968689 A | 06-11-90 |
| | | US 5173495 A | 22-12-92 |
| | | US 5470982 A | 28-11-95 |
| ----- | | | |
| EP 325130 A | 26-07-89 | DE 3801406 A | 27-07-89 |
| | | AU 642127 B | 14-10-93 |
| | | AU 2861789 A | 20-07-89 |
| | | CN 1034364 A | 02-08-89 |
| | | DK 23389 A | 21-07-89 |
| | | FI 93007 C | 10-02-95 |
| | | FI 93007 B | 31-10-94 |
| | | HU 210727 B | 28-07-95 |
| | | HU 208958 B | 28-02-94 |
| | | JP 1216974 A | 30-08-89 |
| | | JP 2558344 B | 27-11-96 |
| | | NO 177005 B | 27-03-95 |
| | | PT 89477 B | 28-02-94 |
| | | US 5006530 A | 09-04-91 |
| | | US 5169857 A | 08-12-92 |
| | | US 5401746 A | 28-03-95 |
| ----- | | | |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/13248

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 444533 A | 04-09-91 | AU 645287 B | 13-01-94 |
| | | AU 7101691 A | 29-08-91 |
| | | CA 2036417 A | 27-08-91 |
| | | HU 210148 B | 28-02-95 |
| | | JP 4211660 A | 03-08-92 |
| | | NZ 237097 A | 23-12-93 |
| | | US 5506219 A | 09-04-96 |
| | | US 5686433 A | 11-11-97 |
| | | US 5691322 A | 25-11-97 |
| EP 603699 A | 29-06-94 | DE 4244029 A | 30-06-94 |
| | | AT 147741 T | 15-02-97 |
| | | CA 2112011 A | 25-06-94 |
| | | DE 59305147 D | 27-02-97 |
| | | ES 2096843 T | 16-03-97 |
| | | JP 6234740 A | 23-08-94 |
| | | US 5409910 A | 25-04-95 |
| EP 796846 A | 24-09-97 | DE 19610932 A | 25-09-97 |
| | | AU 1628097 A | 25-09-97 |
| | | CA 2200175 A | 20-09-97 |
| | | CZ 9700843 A | 15-10-97 |
| | | JP 9255574 A | 30-09-97 |
| | | NO 971269 A | 22-09-97 |
| | | PL 319050 A | 29-09-97 |
| | | SK 36197 A | 05-11-97 |
| US 5169857 A | 08-12-92 | DE 3801406 A | 27-07-89 |
| | | US 5401746 A | 28-03-95 |
| | | AU 642127 B | 14-10-93 |
| | | AU 2861789 A | 20-07-89 |
| | | CN 1034364 A | 02-08-89 |
| | | DK 23389 A | 21-07-89 |
| | | EP 0325130 A | 26-07-89 |
| | | FI 93007 C | 10-02-95 |
| | | FI 93007 B | 31-10-94 |
| | | HU 210727 B | 28-07-95 |
| | | HU 208958 B | 28-02-94 |
| | | JP 1216974 A | 30-08-89 |
| | | JP 2558344 B | 27-11-96 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/13248

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|---|--|
| US 5169857 A | | NO 177005 B PT 89477 B US 5006530 A | 27-03-95 28-02-94 09-04-91 |
| EP 742208 A | 13-11-96 | AU 5763596 A CA 2194481 A WO 9634856 A EP 0769007 A NO 965459 A | 21-11-96 07-11-96 07-11-96 23-04-97 18-12-96 |

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.